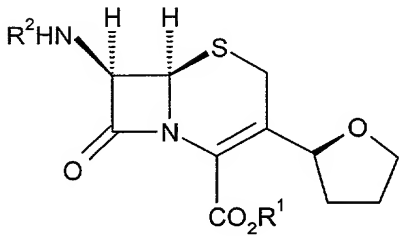
CLAIMS

1. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula **I**:



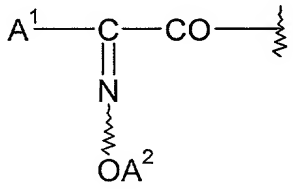
I

or a pharmaceutically acceptable salt thereof,

wherein

the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has the formula:

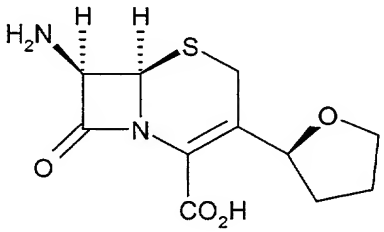


wherein

A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl), and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

comprising reacting a compound of formula **II**:



II

with a compound of the formula **III**:

R^2L **III**;

wherein

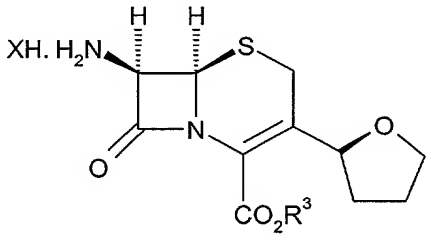
R^2 is as defined above; and

L is selected from the group consisting of hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate,

mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.

2. The process according to claim 1 further comprising the step of preparing said compound of formula **II** by reacting a compound of formula **IV**:

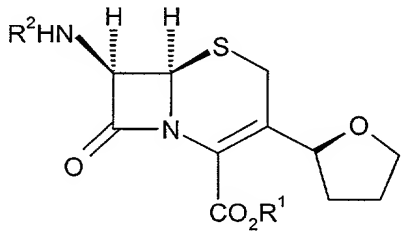


IV

wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a suitable deprotecting agent; in the presence of a solvent.

3. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula **I**:

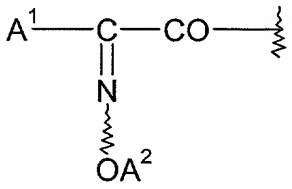


I

or a pharmaceutically acceptable salt thereof,

wherein the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

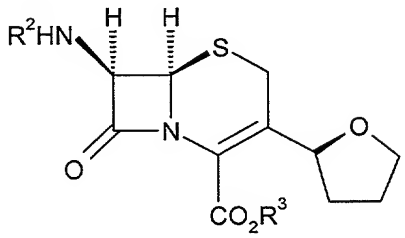
R^2 has the formula:



wherein A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

comprising reacting a compound of formula **V**:

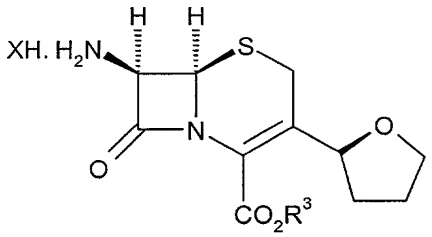


V

wherein R^2 is as defined above; and R^3 is para-nitrobenzyl or allyl;

with a suitable deprotecting agent in the presence of a solvent.

4. The process according to claim 3 further comprising preparing said compound of formula V by reacting a compound of formula IV:



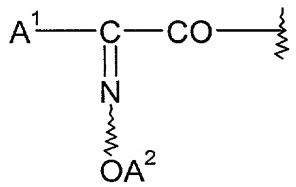
IV

wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a compound of the formula **III**:

R^2L **III**;

wherein R^2 has the formula:



wherein A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl); and

L is selected from the group consisting of hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

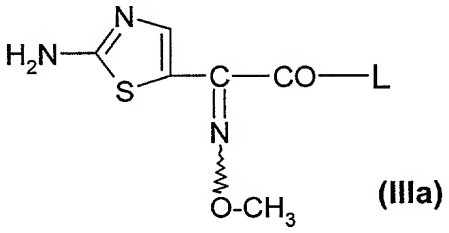
in the presence of a solvent.

5. The process according to claim 1, wherein said A^1 moiety of said R^2 is C_{1-10}heteroaryl selected from the group consisting of furyl, thienyl, pyridyl, aminothiazolyl and aminothiadiazolyl, wherein said amino moiety of said aminothiazolyl or aminothiadiazolyl is optionally protected.

6. A process according to claim 1, wherein said A^2 moiety of said R^2 is C_{1-6}alkyl.

7. A process according to claim 1, wherein L of said compound of the formula **III** is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

8. A process according to claim 1, wherein said compound of formula **III** has a formula **IIIa**:



(IIIa)

and wherein L is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

9. A process according to claim 1, wherein said solvent is water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof.

10. A process according to claim 1, wherein said solvent is water, acetone, or mixtures thereof.

11. A process according to claim 1, wherein a catalyst is used.

12. A process according to claim 11 wherein said catalyst is a Lewis acid catalyst selected from the group consisting of boron trihalide and aluminum halide.

13. A process according to claim 1 wherein said base is diisopropylethylamine or sodium hydroxide.

14. A process according to claim 1, wherein said coupling agent is selected from the group consisting of N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole and N,N'-carbonyldithiazole.

15. A process according to claim 1, wherein said coupling agent is N,N'-dicyclohexylcarbodiimide.

16. A process according to claim 1, wherein said X is chloro.

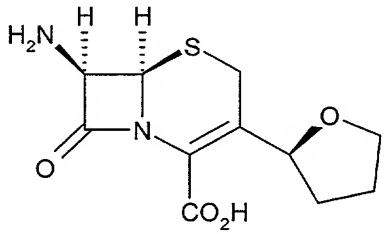
17. A process according to claim 2, wherein said R^3 is para-nitrobenzyl and said suitable deprotecting agent is sodium dithionite or a catalytic hydrogenating agent.

18. A process according to claim 2, wherein said R^3 is allyl and said suitable deprotecting agent is tetrakis triphenylphosphine palladium (0).

19. A process according to claim 17, wherein said solvent is acetone, water, tetrahydrofuran or mixtures thereof.

20. A process according to claim 4, wherein said solvent is methylene chloride, tetrahydrofuran or mixtures thereof.

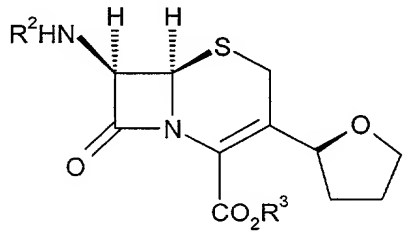
21. A compound of formula **II**:



II.

22. The compound according to claim 21 wherein said compound of the formula **II** has an enantiomeric or diastereomeric purity of 96% to 100%.

23. A compound of formula **V**:



V;

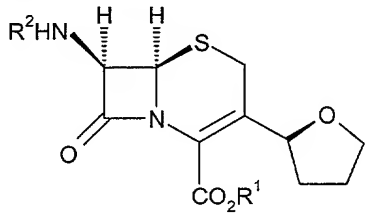
wherein R^2 is acyl; and R^3 is para-nitrobenzyl or allyl.

24. The compound according to claim 23 wherein said compound of the formula **V** has an enantiomeric or diastereomeric purity of 96% to 100%.

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

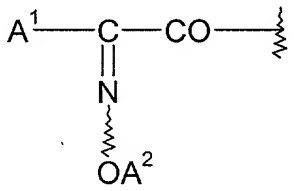
Abstract of the Invention

This invention relates to a novel process for the preparation of 3-cyclic-ether-substituted cephalosporins of formula **I**



I

wherein the group CO_2R^1 is a carboxylic acid or a carboxylate salt and R^2 has the formula:

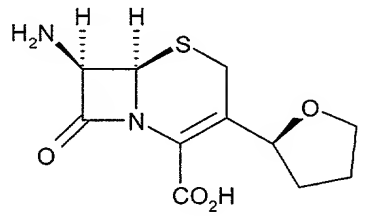


wherein

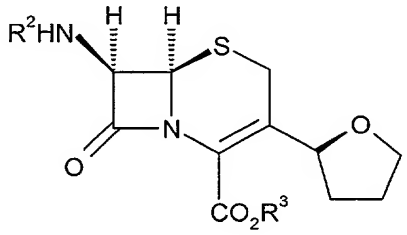
A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

from a zwitterionic compound of formula **II**; or from a compound of formula **V**:



II ;



V;

wherein R^2 is as defined above and R^3 is para-nitrobenzyl or allyl.

The invention also relates to the preparation of the above compounds of formulae **II** and **V**.